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# The power and potential of BIOMAP to elucidate host-microbiome interplay in skin inflammatory diseases

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## Abstract

The two most common chronic inflammatory skin diseases are atopic dermatitis (AD) and psoriasis. The underpinnings of the remarkable degree of clinical heterogeneity of AD and psoriasis are poorly understood and, as a consequence, disease onset

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and progression are unpredictable and the optimal type and time point for intervention are as yet unknown. The BIOMAP project is the first IMI (Innovative Medicines Initiative) project dedicated to investigating the causes and mechanisms of AD and psoriasis and to identify potential biomarkers responsible for the variation in disease outcome. The consortium includes 7 large pharmaceutical companies and 25 non-industry partners including academia. Since there is mounting evidence supporting an important role for microbial exposures and our microbiota as factors mediating immune polarization and AD and psoriasis pathogenesis, an entire work package is dedicated to the investigation of skin and gut microbiome linked to AD or psoriasis. The large collaborative BIOMAP project will enable the integration of patient cohorts, data and knowledge in unprecedented proportions. The project has a unique opportunity with a potential to bridge and fill the gaps between current problems and solutions. This review highlights the power and potential of the BIOMAP project in the investigation of microbe-host interplay in AD and psoriasis.

**KEYWORDS**

atopic dermatitis, biomarkers, microbiome, psoriasis

## 1 | REVIEW OF THE FIELD

### 1.1 | Atopic dermatitis and psoriasis are the most common chronic inflammatory skin diseases

One of the greatest challenges that health systems will face globally in the twenty-first century is the increasing burden of chronic noncommunicable diseases.<sup>1</sup> The skin is an organ often affected by chronic conditions, in particular inflammatory immune-mediated diseases, either as the primary target or through secondary manifestations. The two most common chronic inflammatory skin diseases are atopic dermatitis (AD) and psoriasis.<sup>2,3</sup> Data from the WHO Global Burden of Diseases initiative indicate that at least 230 and 125 million people worldwide have AD and psoriasis (lifetime prevalence 10–15% and 2–3%, respectively<sup>4</sup>), with AD being the leading cause of the non-fatal disease burden conferred by skin conditions.<sup>5</sup> At the patient level, both AD and psoriasis have diverse and marked negative impacts on quality of life (QoL) and place a tremendous financial burden on patients and also on healthcare providers.<sup>6,7</sup> AD and psoriasis are associated with a strongly increased risk of comorbidities. Up to one-third of patients with AD suffer from comorbid atopic diseases, such as food allergy, rhinitis and/or asthma,<sup>8</sup> and up to 20% of psoriasis patients are affected by psoriatic arthritis.<sup>9</sup> Inflammatory bowel disease, rheumatoid arthritis, cardiometabolic traits and neuropsychiatric conditions have also been linked with both AD and psoriasis.<sup>10–14</sup>

AD can manifest at any point in life but the incidence peaks in early infancy, around age 2 years.<sup>15</sup> After onset, the course may be continuous for long periods, but may also show a relapsing-remitting nature.<sup>16,17</sup> Conventional clinical teaching is that AD clears in more than 50% of affected children, but recent data indicate that the proportion of patients with persistent or adult-onset disease, or with relapses after longer asymptomatic intervals, is much higher than previously thought.<sup>18,19</sup>

Psoriasis can also manifest at any age, but onset most commonly occurs between 18 and 39 years and between 50 and 69 years of age.<sup>20</sup> Its natural course is highly variable, but there is little robust epidemiological data on patient trajectories. Both AD and psoriasis are based on a strong inherited predisposition and triggered by environmental factors, ultimately leading to epidermal barrier deficiency and excessive T-cell activation; however, the underlying T-cell polarization is different. Psoriasis is largely driven by Th17 T cells and associated with type 17 responses, and severe disease can effectively be controlled in most patients by blocking the IL-23/Th17 T-cell axis.<sup>21</sup> However, there is significant inter-patient heterogeneity in efficacy and adverse effects to respective biologics, and up to 35% of patients fail their first biologic therapy,<sup>22</sup> possibly reflecting the heterogeneity of the disease. AD has a strong Th2 component but appears to involve multiple immune pathways that might create different disease features.<sup>23,24</sup>

As in many other common chronic inflammatory diseases, the underpinnings of the remarkable degree of clinical heterogeneity of AD and psoriasis are poorly understood and, as a consequence, disease onset and progression are unpredictable and the optimal type and time point for intervention are as yet unknown.<sup>3</sup> Thus, the delineation of disease subtypes and their mechanistic basis and molecular signatures, and biomarkers capable of assessing disease-related individual patient trajectories and response to different therapies are key unmet needs.<sup>3</sup> Ideally, current classifications would be replaced with an aetiology-based taxonomy that can be coupled with effective and safe treatment regimens for AD and psoriasis. Major technological advances in recent years include high-resolution 'omics' assay technologies that enable large-scale multidimensional molecular profiling across biological strata. The intelligent integration of 'omics' data with detailed clinical, environmental and lifestyle information has the potential to identify the molecular identity and subclasses of the underlying disease aetiologies.<sup>25,26</sup> Yet generating,

processing, distributing and utilizing sufficiently large, detailed, reliable and robust sample collections and data sets require complementary expertise and collaborative efforts.<sup>27</sup>

## 1.2 | The human skin microbiome in AD and psoriasis

The human microbiome, that is the assemblage of microbial genomes on or in our bodies, plays an essential role in maintaining our health via crosstalk with the immune system.<sup>28</sup> Representing the largest organ of our body including various distinct physical and chemical niches, the skin presents a diverse environment for microbial growth. Furthermore, being a protective barrier against the external environment, skin constantly receives microbial input from the surroundings, consequently hosting the most diverse microbial communities in the body.<sup>29,30</sup> In healthy skin under steady-state conditions, most microbes thrive as commensals and mutualists, hence interacting with dermal cells in a way that maintains homeostasis of cutaneous immunity.<sup>28</sup> An inadequate barrier function can result from endogenous factors such as filaggrin (FLG) loss-of-function mutations,<sup>31,32</sup> or local inflammation, or from exogenous factors such as bathing practices, and may allow for colonization by opportunistic microbes, triggering an undesirable immune activation. Perturbations in this host-microbe network alter both skin microbiome and immune functions. Whether such shifts are apparent even before disease initiation and can drive disease development have been examined only in small studies<sup>33</sup> but during inflammation, such as in AD, the composition of microbiome often shifts substantially.<sup>34</sup> Shifts in the microbiome composition in psoriasis have also been observed.<sup>35</sup>

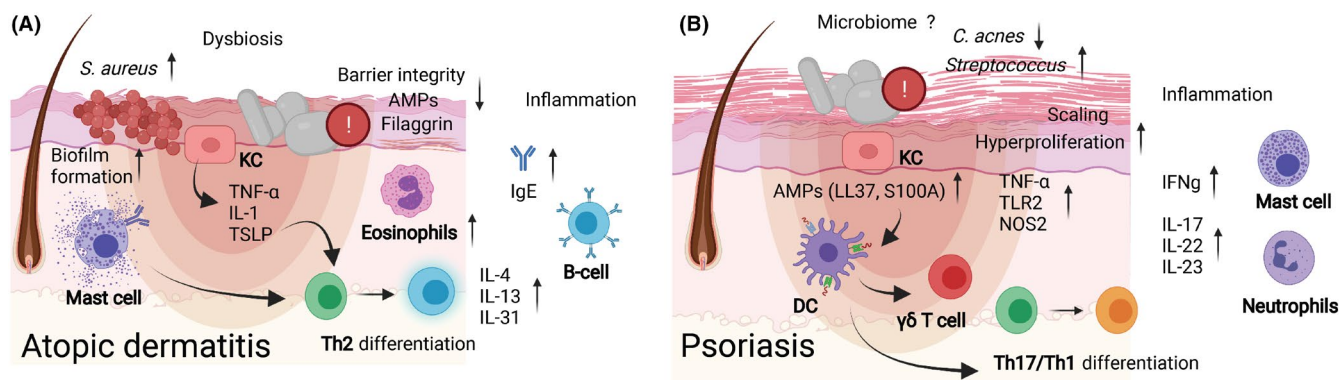
### 1.2.1 | Skin microbiome in AD

The skin microbiome in AD is characterized by increased abundance of *Staphylococcus aureus* (*S. aureus*) and reduced diversity of the

commensal skin microbiome (Figure 1A). Most AD subjects are colonized with *S. aureus*, compared with only 10% of healthy individuals, and the relative abundance of *S. aureus* correlates with disease flares and severity.<sup>34,36–42</sup> *S. aureus* exacerbates AD through mechanisms that affect the epidermal skin barrier as well as cutaneous innate and adaptive immune responses.<sup>43</sup> Staphylococcal enterotoxins act as superantigens to activate polyclonal T-cell responses and can also act as allergens to stimulate IgE production.<sup>44–46</sup> Staphylococcal phenol soluble modulins (PSMs), such as  $\delta$ -toxin which induces mast cell degranulation, and  $\alpha$ -toxin which activates keratinocyte IL-1 $\alpha$  and IL-36 $\alpha$  production are also likely to drive inflammation in AD.<sup>47,48</sup>

Skin microbial diversity is reduced in AD and diversity inversely correlates with disease severity.<sup>34,37,41</sup> Common skin microbiome members, including coagulase-negative staphylococci (CoNS) such as *Staphylococcus epidermidis*, may aid skin homeostasis and protect against the pathogenic effects of *S. aureus*. *S. epidermidis* has been shown to promote TLR2 signalling and antimicrobial peptide (AMP) expression in keratinocytes and also to induce PSM production, which inhibit growth of *S. aureus* in vitro.<sup>49,50</sup> Topical treatment with CoNS in AD resulted in decreased *S. aureus* colonization.<sup>51</sup> CoNS have also been shown to reduce *S. aureus*-driven skin inflammation by producing auto-inducing peptides that inhibit the *S. aureus* accessory gene regulatory quorum sensing system. This resulted in reduced expression of the *S. aureus* virulence factor PSM $\alpha$  in vitro and reduced *S. aureus*-induced skin barrier damage in mice.<sup>52</sup> Furthermore, other skin commensals including *Cutibacterium acnes* and the gram negative *Roseomonas mucosa* have also been shown to inhibit growth of *S. aureus*.<sup>53–55</sup> The homeostasis-inducing properties of these commensal species could potentially be harnessed therapeutically to reduce inflammation and treat AD in the future.

It remains largely unknown whether certain microbial populations in the skin precede or protect from the development of AD, though many of the environmental factors that have been associated with protection from AD development, such as rural living environment<sup>56</sup> and exposure to dogs,<sup>56</sup> are potential seeding sources for the skin microbiome.<sup>57</sup>



**FIGURE 1** Host-microbe interactions are implicated in the pathogenesis of atopic dermatitis and psoriasis. Schematic view of alterations in the skin microbiota and host defence responses in (A) atopic dermatitis and (B) psoriasis. AMPs = antimicrobial peptides, DC = dendritic cell, KC = keratinocyte, Th = T helper cell, IL = interleukin, TSLP = thymic stromal lymphopoietin, TNF = tumour necrosis factor alpha, IFN $\gamma$  = interferon gamma, TLR2 = toll-like receptor 2 and NOS2 = nitric oxide synthase 2

### 1.2.2 | Skin microbiome in psoriasis

In contrast to the established association between AD and *S. aureus*, knowledge regarding the skin microbiome in psoriasis is more nascent.<sup>58,59</sup> There is a clear connection between psoriatic flares and microbial alterations, suggesting that skin microbiota may be an important player in the aetiology of this disease. However, no specific microbial patterns have been possible to determine, due to conflicting results from several studies. Nevertheless, a common observation in psoriatic skin is the underrepresentation of certain taxa, such as *Cutibacterium acnes* (Figure 1B), which are highly abundant in healthy skin. Moreover, some studies have reported the overrepresentation of *Streptococcus* species,<sup>60-62</sup> and others have described the association of *Staphylococcus* species with the disease.<sup>58,63</sup> Like *S. aureus*, *Streptococcus* species can secrete superantigens which stimulate T-cell expansion, potentially leading to the breakdown of immune tolerance to cutaneous microbes, and the accumulation of Th1 and Th17 cells.<sup>64</sup>

## 1.3 | Lifestyle, environment variables and genetic factors associated with the human microbiome and inflammatory skin disease

### 1.3.1 | Lifestyle and environment in the general population

The very first scaffold of the human skin microbiome is already set at birth and impacts health and disease via early influences on the developing immune system.<sup>65,66</sup> During puberty, the change in hormones and sebum expression in the skin leads to a profound change in the microbial composition of the skin,<sup>67</sup> which then remains largely stable during adulthood, despite lifelong exposure to strongly fluctuating environmental factors.<sup>68</sup> To better understand the fundamental forces that shape the healthy skin microbiota, several studies have investigated the impact of lifestyle and environmental factors on the microbial skin community in the general population. These studies have shown that the strongest influence on the skin microbiome stems from the local skin microenvironment, in particular determined by skin pH, skin hydration, sebum production and epidermal lipid content.<sup>69,70</sup> Additionally, links between the skin microbiome or its members and a variety of intrinsic and extrinsic factors have been observed, including age,<sup>57,71,72</sup> sex,<sup>73,74</sup> BMI,<sup>75</sup> use of cosmetic products,<sup>76,77</sup> exposure to antibiotics,<sup>78</sup> ethnicity and geographical region.<sup>79-81</sup> Moreover, variation in the skin microbiome was found to be associated with several environmental factors, including UV exposure,<sup>82</sup> exposure to domestic animals such as dogs,<sup>83</sup> contact with soil and plants,<sup>84</sup> and urbanization of place of residence.<sup>57,85</sup> While many of these results have been replicated in independent studies (eg age), our current understanding is still patchy, with few studies available that aimed to integrate many candidate factors.<sup>71,74</sup>

### 1.3.2 | The effects of the environment on the microbiome and the skin-gut axis in AD and psoriasis

There is increasing recognition of the global burden of both AD and psoriasis, with changing epidemiological patterns in high- and low-income countries.<sup>86,87</sup> Both diseases are more prevalent in high-income and in highly westernized countries, but the exact relationship between environmental risk factors and AD and psoriasis remains to be elucidated. Epidemiological studies have implicated hygiene-related factors, urbanization and climate, which are thought to reduce microbial biodiversity, and lifestyle factors, such as diet and obesity, alcohol, smoking and stress, which may impact chronic inflammation.<sup>88</sup>

The International Study of Asthma and Allergies in Childhood (ISAAC) studies contributed significantly to our understanding of the global prevalence of AD, and the changing patterns amongst high- and low-income countries.<sup>88-91</sup> There is conflicting evidence regarding the geographic distribution of psoriasis with some studies reporting higher incidence and prevalence rates of psoriasis with increasing distance from the equator.<sup>92,93</sup> However, this relationship was not confirmed in a recent systematic review and meta-analysis,<sup>87</sup> which attributed increased frequency of psoriasis to higher income levels. Urbanization, air pollution and differences in climate and UV exposure are possible explanations for increased frequency of AD and psoriasis at higher latitudes. Lower UV exposure directly contributes to lower vitamin D levels, which may be relevant to AD and psoriasis given their associations with hypovitaminosis D.<sup>94,95</sup> Vitamin D affects the innate and adaptive immune system, antimicrobial defences and influences skin barrier function.<sup>95,96</sup> UV radiation has been shown to impact the skin microbiome in healthy volunteers,<sup>82</sup> and phototherapy modifies the skin microbiome in patients with psoriasis<sup>97</sup> and with AD.<sup>98</sup> Narrowband UVB and natural sunlight exposure on the skin may even modulate the gut microbiome.<sup>99,100</sup> The skin, gut and household microbiome varies amongst populations living in regions with the same latitude, but varying levels of urbanization. These changes, particularly changes in the mycobiome, are associated with availability of household cleaning products and dwelling type.<sup>85</sup> Further research integrating the impacts of the environment, including temperature, climate, pollution and urbanization, on the skin and gut microbiome and the relationship with AD and psoriasis is required.

In addition to environmental factors associated with urbanization, a Western lifestyle, diet and increasing obesity may play a role in AD and psoriasis.<sup>101,102</sup> Patients with psoriasis are at significantly increased risk of metabolic diseases including hyperlipidaemia, insulin resistance, obesity and the metabolic syndrome.<sup>103-105</sup> Mendelian randomization has shown that obesity plays a causative role in psoriasis.<sup>106</sup> The relationship between diet and the gut microbiome is bidirectional<sup>107</sup>: nutrient availability impacts the bacterial community structure and the metabolic effects of the gut microbiome influence the host's energy availability and alter the metabolome.<sup>108</sup> The health consequences of an obesity-associated gut microbiome

have been discussed elsewhere,<sup>109–111</sup> and associations between the skin microbiome and obesity and diet have more recently been reported.<sup>75,112</sup> Whether the gut and/or skin microbiome have mediating, confounding or bystander roles in the relationship between psoriasis and/or atopic dermatitis and obesity remains to be fully elucidated.

### 1.3.3 | Genetics

The influence of human genetics on the skin microbiome is largely understudied, particularly at the general population level, and available AD studies have mainly focused on mutations in the skin barrier gene filaggrin (FLG). In a seminal work, Si et al.<sup>113</sup> found that the heritability of bacterial clades ranged from 40.9% to 56.4% in a study of 45 individuals, including twins. In addition, they found an association between a single nucleotide polymorphism (SNP) in the FLG gene when searching within a SNPs panel of skin-related genes. FLG encodes a structural protein essential for skin barrier function,<sup>32</sup> and its loss-of-function mutations are the strongest known genetic risk factors for AD<sup>31,114</sup> and the cause of ichthyosis vulgaris.<sup>115</sup> FLG mutations have been associated with distinct skin microbiome profiles of healthy individuals, which instead resembled microbiome profiles observed in AD patients.<sup>116</sup> Furthermore, FLG mutations were associated with *Staphylococcus aureus* colonization in AD patients<sup>117</sup> and microbial composition in patients' non-lesional skin.<sup>118</sup> Nevertheless, to the best of our knowledge, no systematic survey of possible influences of genes on the skin microbiome has been conducted on the general population nor on patients with AD or psoriasis. This is in strong contrast with the increasing number of genome-wide association studies conducted on gut microbial communities (mGWAS), which now include thousands of participants.<sup>119,120</sup> The interaction between host genetics and gut microbiomes found by mGWAS studies suggest that such interactions may exist for the skin microbiome. Further findings are, however, more suggestive of a potential impact of host genetics on skin microbiome, such as microbiome-related gene expression profiles of psoriasis patients and AD patients,<sup>121–123</sup> the association of skin bacterial communities with ethnicity,<sup>81</sup> and the small proportion of microbial community variation explained by individual, lifestyle and environmental factors combined (around 15%).<sup>76</sup>

## 1.4 | Disease initiation and early AD development

The healthy skin microbiota changes considerably throughout life, with *Staphylococcus* and *Streptococcus* dominating in infancy, while *Cutibacterium* and *Corynebacterium* are more abundant in adulthood (Figure 2A).<sup>67,70,124,125</sup> Interestingly, the prevalence of AD is highest in the first years of life, with a considerable decline around school age<sup>126,127</sup> (Figure 2B), and while AD can resolve in some cases, for others it becomes a lifelong condition.<sup>86</sup> Interestingly, the skin microbiota in young children is also quite different from that

of older children and adults.<sup>67,70,124,125</sup> This could suggest an age-specific skin dysbiosis in infant lesional skin (Figure 2C), a hypothesis that is supported by a few studies, each with low numbers of participants.<sup>122,128</sup> Skin barrier dysfunction, including that caused by filaggrin mutations, is associated with immunological Th2 skewing,<sup>86</sup> but this relationship is bidirectional as Th2 inflammatory cytokines (such as IL-4, IL-13 and IL-33) can directly disrupt the skin barrier, through alterations in filaggrin breakdown products and stratum corneum lipid mediators.<sup>129,130</sup> It is not known how microbial exposures in early life interact with genetic and environmental factors in the initiation of AD. As discussed previously, pathogenic bacteria can, themselves, impair the skin barrier by producing superantigens and toxin-promoting biofilms, and by inducing thymic stromal lymphopoietin.<sup>131–133</sup>

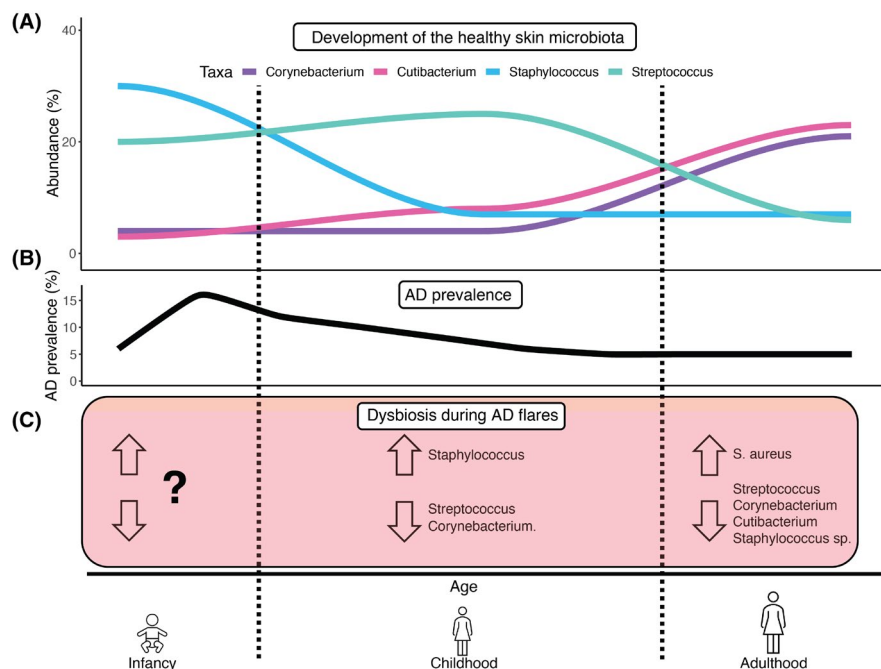
### 1.4.1 | Early life is a critical window for immune-microbe interactions

Birth marks the abrupt transition from intra-uterine to postnatal life, a period characterized by dynamic changes in the infant's living environment, colonizing microbiota and their immune system. Our understanding of the infant's developing immune system has evolved, with some authors, suggesting that it should be considered specialized rather than immature.<sup>131–133</sup> Early life is a 'window of opportunity' for the development of a symbiotic relationship between the host immune system and colonizing microbes.<sup>134,135</sup> Initially, maternal passive immunity predominates and the infant's adaptive immune system is characterized by high levels of tolerogenic regulatory T lymphocytes (Tregs).<sup>136</sup> Requirements for skin biopsies hinder our understanding of the infant's cutaneous immune system; however, mouse models suggest early exposures to commensal bacteria may entrain a population of skin-resident Tregs.<sup>137</sup> Culture-based<sup>138</sup> and culture-independent microbiome studies<sup>125</sup> in human infants demonstrated that perturbations of the early-life skin microbiome, including differential colonization with commensal staphylococcal species, can influence the subsequent development of AD.

### 1.4.2 | The infant gut microbiome and AD

To date, studies of the microbiome in early life have primarily focused on the gut.<sup>139–144</sup> The Environmental Determinants of Diabetes in the Young (TEDDY<sup>139</sup>) study provides the largest longitudinal microbiome data set from early life to date ( $n = 903$ ) and demonstrated that breastfeeding was the major determinant of gut microbiome maturation. The TEDDY study and others have identified associations between the infant gut microbiome and mode of delivery,<sup>145</sup> antibiotic exposure,<sup>146–148</sup> geographical regions, and the presence of older siblings<sup>140,149</sup> and household pets,<sup>150</sup> factors which have also been associated with AD in epidemiological studies.<sup>86</sup> Further recent evidence comes from the Enquiring About Tolerance (EAT) cohort; caesarean section and the early introduction of solid foods alongside





**FIGURE 2** The development of the skin bacterial community structure and the nature of perturbations during AD lesions in different developmental periods. A, Schematic view of the healthy developing skin microbiota, shown through the relative abundance of the four most prevalent bacterial genera present on the skin during infancy, childhood and adulthood. B, Schematic view of the prevalence of AD during infancy, childhood and adulthood, highlighting that the major disease burden of AD occurs in early life. C, The red box marks the age-specific dysbiosis associated with lesional AD skin, resulting in higher (up-arrow) or lower (down-arrow) relative abundances of certain bacterial genera. The nature of this dysbiosis in infancy is largely unknown and is therefore marked with a question mark

breastfeeding had the strongest impact on the evolution of the gut microbiome.<sup>151</sup> In addition, increased *Clostridium sensu stricto* relative abundances at three months of age were associated with the presence of AD at three and twelve months of age. However, a previously published systematic review<sup>152</sup> did not find a consistent association between the diversity of the gut microbiome and the development of AD, nor a consistent association of specific bacterial species with AD. The heterogeneity of results may be attributable to methodological and technical differences between studies.

#### 1.4.3 | The early-life skin microbiome requires further research

The microbiome of the skin and other body compartments has increasingly been studied, including in early life. Chu et al.<sup>65</sup> demonstrated minimal site specificity of the microbiome of the meconium, nostrils, oral cavity and skin when sampled immediately after birth. However, by 6 weeks of age, the infant's microbiome had developed distinct ecological niches.<sup>65</sup> Site-specific differences of the skin microbiome can be detected as early as the second day of life,<sup>125</sup> reflecting age-related and topographic differences in skin physiology, barrier function<sup>153,154</sup> and micro-environments.

Mode of delivery may exert a small influence on the skin microbiome at birth, but this influence appears to be short-lived.<sup>65,125</sup> Small studies have examined the influence of gestational age, antibiotic

exposure<sup>155</sup> and feeding<sup>125</sup> on the early-life skin microbiome but the long-term effects in shaping the infant skin microbiome are not clear. A small study of infants at risk of AD demonstrated differences in the skin microbiome and the skin pH in those randomized to use daily emollients.<sup>156</sup> A larger randomized trial evaluating the use of emollients<sup>157</sup> for the prevention of AD demonstrated a trend towards higher skin infection rates but did not specifically characterize the skin microbiome. Infant bathing practices have been demonstrated to influence skin barrier<sup>158</sup> function; however, the effects of bathing and hygiene practices on the infant skin microbiome have not been characterized.

#### 1.4.4 | The gut-skin axis in early life

Beyond taxonomic classification, the functional roles of the gut and skin microbiota in AD have not been established. Metagenomic and metabolomic studies of the gut microbiome have identified associations with AD,<sup>159,160</sup> and a variety of other diseases including allergic sensitization, asthma,<sup>161,162</sup> inflammatory bowel disease<sup>163</sup> and obesity.<sup>164</sup> For example, bacterial-derived short-chain fatty acids can exert anti-inflammatory or tolerance-inducing effects.<sup>165,166</sup> In culture-based studies,<sup>167,168</sup> early gut colonization with particular *Staphylococcus aureus* strains was negatively associated with later development of AD. The metabolic impact and immunologic consequences of the skin microbiome in early life, and the relationship

with the initiation and early development of AD and other atopic diseases remains to be defined. It is plausible that there is crosstalk between the infant gut and skin microbiota and the developing immune system.

## 1.5 | Gene-microbiome networks underlying cutaneous inflammation

Abnormal host-microbe interactions are associated with cutaneous disorders like AD and psoriasis,<sup>34,60,125,169</sup> but little is known about their physiological roles and the molecular mechanisms that mediate cutaneous host-microbe interactions. Meisel et al.<sup>170</sup> profiled the skin transcriptome of mice in the presence and absence of microbiota to identify genes and pathways under transcriptional modulation by the microbiome. They used germ-free (GF) mice and compared their dermal transcriptome to that of conventionally raised mice (SPF). In the presence of microbiota, close to 3000 genes were differentially expressed between GF and SPF skin. Innate immune response genes and genes involved in cytokine signalling were generally upregulated in response to microbiota and included genes encoding toll-like receptors, antimicrobial peptides, the complement cascade, and genes involved in IL-1 family cytokine signalling and homing of T cells. Their results also revealed a role for the microbiota in modulating epidermal differentiation and development, with differential expression of genes in the epidermal differentiation complex (EDC).<sup>170</sup>

### 1.5.1 | The *S. aureus*-related host gene signature in AD

Only very few studies have investigated the interplay between skin microbiota and host cutaneous transcriptomes in patients with inflammatory skin diseases. To achieve a better understanding of the dialogue between the skin and its microbiome, we correlated the relative abundance of skin microorganisms to host cutaneous transcriptomes in study subjects of the large MAARS cohort (belonging to the BIOMAP cohort portfolio), including patients with AD ( $n = 82$ ) and psoriasis ( $n = 119$ ), and healthy volunteers (HV,  $n = 115$ ).<sup>122</sup> We stratified AD patient samples into 'high' and 'low' groups, based on *S. aureus* abundance. Comparison of the transcriptomes between *S. aureus* high and low samples revealed a set of 256 significant genes. To explore whether the *S. aureus*-regulated genes were relevant to global features of AD pathophysiology, we created a co-expression network based on AD-associated genes, and partitioned the network into functional modules based on the expression patterns. Projecting *S. aureus*-regulated genes onto the AD network revealed significant enrichment in genes that mapped to modules associated with keratinocyte differentiation and extracellular matrix organization. Functional analysis of the *S. aureus*-regulated genes revealed the enrichment of keratinization and skin development, TH17 signalling and tryptophan (trp) degradation.<sup>122</sup> Unlike in AD, where one species, *S. aureus*, was identified as the dominant microbe, psoriasis

is characterized by co-occurring communities of microbes with weak associations with disease-related gene expression.<sup>122</sup> The MAARS study represents a rich data set giving an opportunity for further detailed analysis of specific microbe-host interaction.

Altunbulakli et al.<sup>121</sup> similarly used an integrated 'omics' approach to uncover possible correlations between the skin microbiome and the skin transcriptome in the context of AD. They performed genome-wide RNA sequencing (RNAseq) and 16S rRNA gene sequencing of skin samples collected from patients with AD and from healthy subjects (HV), showing that the *Staphylococcaceae* family significantly increased in abundance in patients with AD. Furthermore, comparison of the skin transcriptomes between AD lesional and healthy skin, revealed that cell adhesion, cadherin signalling and keratinization were amongst the most differentially expressed gene groups in patients with AD.<sup>121</sup> Finally, the frequency of *Staphylococcus* species correlated with dysregulation of the skin barrier related genes in patients with AD. In particular, in lesional skin there was a correlation between the relative abundance of all major *Staphylococcus* species (*S. aureus* negatively and *S. epidermidis*, *S. hominis*, and *S. haemolyticus* positively) and the expression of tight junction genes.<sup>121</sup>

### 1.5.2 | Association between *S. aureus* abundance, disease severity and dermal gene expression in different skin sites

Very few microbiome and transcriptome studies have explored AD heterogeneity between skin sites, with most studies focusing on a single site or pooled samples from different body sites for statistical analyses. Since the anatomical location is known to be a strong determinant of the microbial composition in healthy individuals,<sup>171</sup> local skin physiology could determine the role of the microbiota in AD in a skin site-dependent fashion. In order to investigate further the interaction between host and skin microbiome in AD, we examined two physiologically distinct body sites: posterior thigh and upper back in the MAARS cohort.<sup>123</sup> Transcriptome analysis revealed distinct disease-related gene expression profiles depending on anatomical location, with keratinization dominating the transcriptomic signatures in posterior thigh, and lipid metabolism in the upper back. To investigate links between *S. aureus* colonization and transcriptional profiles, lesional skin samples in thigh were stratified into 'high' and 'low' groups, based on *S. aureus* abundance. This resulted in the identification of about 100 significant genes and functional enrichment of biological processes such as keratinization and epidermal cell differentiation, as well as circadian regulation. The relative abundance of *S. aureus* and *S. epidermidis* displayed an inverse correlation in lesional skin of the thigh. The abundance of *S. aureus* was also positively correlated with disease severity. Weighted correlation network analysis (WGCNA) identified two modules correlating positively with the abundance of *S. aureus* and *S. epidermidis*, respectively. The *S. aureus* associated module displayed enrichment of extracellular matrix organization and leukocyte migration. Instead, the *S. epidermidis*-associated module exhibited enrichment of epidermal development and was associated with computationally estimated mast cell fraction in the skin. Considering the



inverse relationship between *S. aureus* and *S. epidermidis* abundances in the lesional skin sites, *S. epidermidis* might play a role in mast cell function, potentially explaining the milder form of disease compared to that in *S. aureus*-dominated skin flares.<sup>123</sup> These findings suggest that in AD, the skin microbiota interacts through local, host-driven mechanisms, forming different ecological niches and thereby distinct microbe-host interactions, which should be taken into account when considering treatment options.

### 1.5.3 | Associations between *Streptococcal* species and the immune system in psoriasis

As proposed already in 1995,<sup>172</sup> acute guttate psoriasis is initiated by  $\beta$ -haemolytic streptococcal isolates colonizing throat and secreting superantigen M-protein, a major virulence factor. T cells that recognize M-protein determinants in the palatine tonsils and keratin determinants in the skin that are homologous to M-protein may then potentially play a role in chronic disease,<sup>173</sup> a notion supported by the finding that streptococcal infection precede acute psoriasis and are associated with exacerbations of chronic plaque psoriasis.<sup>174-176</sup> Streptococcal peptidoglycan (PG) was also proposed to participate in p by binding to innate immune receptors.<sup>173</sup> In addition, PG-containing cells were detected to be increased in chronic plaque skin lesions and associated with PG-specific CD4+ T cells.<sup>177</sup>

## 2 | THE BIOMAP PROJECT

### 2.1 | BIOMAP—Biomarkers in atopic dermatitis and psoriasis

Funding agencies have widely embraced collaborative funding models for research consortia such as the large-scale Innovative Medicines Initiative (IMI). IMI is a public-private partnership that aims to improve health by speeding up the development of innovative medicines, particularly in areas where there is an unmet medical and/or social need. IMI is the world's biggest public-private partnership in the life sciences. The partnership includes the European Commission (EC) (representing the EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) (representing pharmaceutical industry partners), and is supported by these two parties. Industry partners contribute to the projects in a variety of ways, including bringing in-kind consortium capacity and knowhow, while the EC matches the overall value of these contributions to fund activities provided by academia, small- to medium-sized enterprises, and other non-industry groups.<sup>178</sup> Since 2006, the IMI has funded more than 120 projects with more than 1.5 billion € of EU funding focused on major diseases affecting European citizens.

However, it took until 2019, when BIOMAP (Biomarkers in Atopic Dermatitis and Psoriasis) was launched under the grant agreement No. 821511, for the first IMI project to specifically focus on skin diseases. The BIOMAP consortium includes 7 large pharmaceutical companies and 25 non-industry partners including academia, small- to

medium-size enterprises, and patient advocacy groups (<https://www.biomap-imi.eu/>). A total of 8 work packages (WPs) collaborate in an integrated manner in order to understand key mechanisms and pathways that operate in AD and psoriasis and to re-classify these diseases based on their intrinsic biology ('endotypes'), and to identify molecular signatures, which have the potential to be developed into biomarker assays. BIOMAP brings together clinical and molecular data as well as high-quality biological samples from large-scale existing patient collections, disease registries, epidemiological studies and clinical trials, to then complement and integrate molecular data on existing samples across multiple scales from pathways to cells and tissues, and link them to relevant and sufficiently detailed readouts. A series of 'omics' data (in particular, genomics, transcriptomics, methylomics, proteomics and microbiomics) will be analysed on coordinated sets of samples in order to provide insight into the basic biological properties reflected by these data. To support appropriate harmonization and interpretation of molecular information, BIOMAP has established a glossary of clinical phenotypes and key outcomes,<sup>179</sup> making use of existing international initiatives and consensus exercises, and integrating the patient (and their careers) view by capitalizing on the reach of partnering patient organizations.

Since there is mounting evidence supporting an important role for microbial exposures and our microbiota as factors mediating immune polarization and AD and psoriasis pathogenesis, flares and chronicity, an entire BIOMAP work package is dedicated to the investigation of skin and gut microbiome linked to AD or psoriasis. Microbiome research in this area has been more focused on AD but remains fairly limited for both diseases. In addition to microbial patterns and signatures associated with AD and psoriasis, BIOMAP investigates potential disease subtypes based on microbial heterogeneity. Furthermore, variability across time scales due to disease- and disease activity-related changes, and host molecular constituents related to normal and pathological shifts will be dissected.

### 2.2 | Aims and perspectives of the BIOMAP project related to host-microbe interplay

Our efforts in investigating the causes and mechanisms of AD and psoriasis, in identifying biomarkers which may be responsible for the variable disease outcome, and in understanding the role of the human microbiota in disease pathogenesis are summarized in Figure 3. In the subsections below we list main aims of the BIOMAP project.

#### 2.2.1 | Expand current knowledge regarding AD and psoriasis-associated microbiomes and their role in pathogenesis

To date, most microbiome studies have been relatively small, with cohorts that include different disease subtypes. The inherent heterogeneity of skin inflammation, disease diagnostic criteria and the skin microbiome makes it difficult to draw firm conclusions from these small

studies on differences in the microbiome between health and disease. Moreover, the lack of sufficiently sized longitudinal studies hampers the possibilities to gain insight into causality. In addition, significant variability in the methods used to study the skin microbiome has made comparing findings between studies difficult and limits the potential that can be learned from these studies.<sup>180,181</sup> The BIOMAP consortium has the opportunity to integrate information from several large paediatric and adult cohorts, while accounting for these sources of variation, to more precisely determine the microbiome in psoriasis and AD. 16S rRNA gene amplicon data from several BIOMAP cohorts will be harmonised, allowing standardization across studies for downstream analysis steps. Moreover, the choice of 16S rRNA primer pair(s) will be carefully considered.<sup>181</sup> In parallel with 16S rRNA gene sequencing, the large MAARS cohort within BIOMAP uses whole metagenomic shotgun (WMS) sequencing to study the microbiome in AD and psoriasis.<sup>122</sup> The BIOMAP WMS data will provide species- and strain-level taxonomic information for eukaryotes, prokaryotes as well as viruses and enable the profiling of their functional potential. Constructing microbial genomes from WMS and contrasting their functional potential associated with diseased and healthy skin will provide us further mechanistic insights into how the skin microbiome may function in AD and psoriasis.

### 2.2.2 | Improve our knowledge regarding the influence of lifestyle and environmental exposures on the human microbiome and disease risk

BIOMAP connects the cross-sectional population-based cohorts from the north of Germany (PopGen) and south of Germany (KORA FF4 and KORAFIT), each including hundreds of participants from

whom skin swabs were taken for 16S rRNA gene amplicon profiling. Rich information on participant's lifestyle and environmental exposition was collected. Furthermore, participants have or are being genotyped, allowing for the investigation of the relationship of host genetics and the skin microbiome by mGWAS. BIOMAP also includes a longitudinal birth cohort from the South of Germany (KUNO), and deeply phenotyped and methodologically aligned birth cohorts from the UK (EAT) and Denmark (COPSAC), with microbial samples collected before onset of disease. Collectively, these studies provide the opportunity to assess the effects of lifestyle and environment on the microbiota of the skin and gut and their intersection with inflammatory skin diseases. The analysis of these cohorts has the potential to provide a more comprehensive view of the associated factors and the discovery of small effects due to the integrative analysis of many candidate factors and increased statistical power. Moreover, the integration of independent cohorts allows for replication of results, and therefore, generalization of the outcomes. An example of such potential is the recent publication under BIOMAP (Moitinho-Silva et al.<sup>182</sup>), in which a detailed analysis of lifestyle and environmental factors was carried out with PopGen and KORA FF4 cohorts, leading to insights into the forces possibly shaping the skin microbiome and the discovery of its associations with diet.

### 2.2.3 | Provide novel insights into disease initiation and early AD development

The dynamic changes of the skin microbiome during infancy, childhood and around puberty, followed by the relative stability<sup>68</sup> during

**FIGURE 3** Potential outputs of the BIOMAP project. The IMI Consortium dedicates an entire work package to host-microbiome interplay in atopic dermatitis and psoriasis, with the potential to provide novel insight into disease mechanisms and classification, novel treatments and strategies for disease prevention. In a large-scale and well-coordinated manner, BIOMAP partners bring together biological samples, clinical information and 'omics' data from existing patient collections to be integrated with skin and gut microbiomes. Using this collaborative approach accompanied with data harmonization and standardized analysis strategies, BIOMAP pursues to answer open questions in the field

#### Outstanding questions



#### BIOMAP goals and solutions

Large and robust sample collections with detailed clinical data

Large-scale molecular and microbial profiling of AD and psoriasis

Developing a gold standard for microbiome analysis

↳ **Etiology-based disease classification, safe and efficient therapy**

Longitudinally sampled birth-cohorts, profiling the microbiome before and after disease onset

Systematic survey of human genetics, microbiota and disease outcome

Integration of large sample collections with clinical, environmental and lifestyle data, including early-life events

Mechanistic validation in relevant in vitro models

↳ **Novel strategies for disease prevention**

adulthood, raise the possibility that perturbations of the early-life skin microbiome<sup>68</sup> could have long-lasting effects. A better understanding of the factors influencing the early-life skin microbiome may provide insights into the relationship between hygiene-related environmental exposures and the increasing global incidence of AD and allergic diseases, as well as guiding novel preventative and therapeutic strategies for AD.

BIOMAP offers an exciting opportunity to study the early-life skin and gut microbiome, its determinants, and its effects on the later development of AD and other allergic diseases. In addition to information available from a longitudinal birth cohort from the South of Germany (KUNO), BIOMAP is supporting the collaborative analysis of two deeply phenotyped longitudinal birth cohorts, the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC<sub>2010</sub>) mother-infant cohort<sup>183</sup> and the participants of the Enquiring About Tolerance (EAT) randomized clinical trial.<sup>184</sup> Unselected infants in these independent studies underwent longitudinal sampling of both the skin and gut microbiota before the onset of disease, alongside detailed reporting of environmental exposures, clinical phenotyping during childhood and systematic evaluation of disease outcomes with predefined diagnostic criteria for AD. A collaborative approach, using standardized laboratory and analytical pipelines, will facilitate comparisons and replication of findings between these cohorts, aiming to identify possible microbial alterations that precede the development of AD.<sup>138</sup> We will also examine for any infant-specific dysbiosis of eczematous skin lesions (Figure 2B,C), and finally, we will investigate whether there are specific bacterial biomarkers that predict disease persistence and/or severity in later life.

The dynamic changes of the skin microbiome during infancy, childhood and around puberty, followed by the relative stability<sup>68</sup> during adulthood, raise the possibility that perturbations of the early-life skin microbiome<sup>68</sup> could have long-lasting effects. A better understanding of the factors influencing the early-life skin microbiome may provide insights into the relationship between hygiene-related environmental exposures and the increasing global incidence of AD and allergic diseases, as well as guiding novel preventative and therapeutic strategies for AD.

#### 2.2.4 | Explore pathomechanisms of host-microbe interplay in AD and psoriasis, using cutting-edge bioinformatics and omics technologies

The involvement of streptococci in psoriasis suggests that there could be the interplay between microbes and host genes in psoriatic skin. Moreover, WMS data have shown that *S. epidermis* strains specific to psoriasis lesions produced virulence factors in lesions but not in unaffected skin implying that there could be microbial participation in psoriasis skin beyond *Streptococcus*.<sup>185</sup> However, the knowledge on gene-microbe interactions in skin is still scarce. To our knowledge, only the MAARS cohort belonging to BIOMAP<sup>122</sup> has utilized the integration of psoriatic skin microbiome and transcriptome

and found weak associations, and no study to date has integrated transcriptome and microbiome for non-lesional and lesional sites separately. Furthermore, there are no studies investigating interactions between host genes and microbial functional genes, which requires WMS. WMS is also required for detecting strain heterogeneity between lesional and non-lesional sites, recently proposed<sup>185</sup> and gene-microbe strain level associations.

The easy accessibility of skin makes it an excellent target for simultaneous sampling of the microbiome and host tissue samples from exactly the same anatomical location to explore the relationship between the skin microbiome, gene regulation and disease activity within the BIOMAP project. During the life course of BIOMAP, we will expand our focus from 16S rRNA gene amplicon sequencing to metagenomics, which is already available in some of the BIOMAP cohorts (eg MAARS) and integrate it with genetic and skin transcriptomics data. Taking advantage of the multiple data layers (eg microbiome, transcriptome and methylome), we have the possibility to address the interplay between specific microbes or their functional properties and host tissue responses in AD and psoriasis.

#### 2.2.5 | Explore host-microbe interplay by using disease relevant ex vivo and in vitro models

To take full advantage of the unprecedented BIOMAP resource and framework for the discovery of molecular interactions within the human cutaneous ecosystem, key findings of large-scale analyses can be validated and characterized in further detail using both ex vivo and in vitro experimental setups. These studies may not only aid in the identification of host responses to individual pathogenic or commensal microbial strains, but can also model the interaction of several key microbial species on the skin surface. Complex and tissue-like 3D human skin or epidermal equivalent models (HSEs and HEEs, respectively) are favourable compared to keratinocyte monolayer cultures, especially in validating *in vivo* findings on both inflammatory responses and specific host-microbe interaction pathways. The advantage of a functional skin barrier and presence of a stratum corneum enable the faithful mimicking of both environmental and internal factors.<sup>186</sup> Although bacterial or fungal co-culture approaches seem rather straightforward,<sup>187</sup> the modelling of long-term interactions and intervention studies are limited by technical challenges, while donor-dependent differences limit the power to detect meaningful interactions. Therefore, standardized experimental models with defined genomic background amenable for genome editing, co-culture, omics sampling and longitudinal biophysical measurements are in high demand. The immortalized N/TERT keratinocytes could provide such a resource given their high similarity to primary keratinocytes<sup>188</sup> and accurate disease modelling using CRISPR-Cas technology.<sup>189</sup> Co-cultures of organotypic skin models with a selection of key microbial species and strains identified in multi-omics analysis within the BIOMAP framework can provide detailed insights into molecular interactions, and possibly guide further research into the 'homeostatic' skin microbiota.

## 2.3 | Conclusions

Despite the significant advance in our current understanding of the human skin microbiome and skin inflammatory diseases, many questions remain. What are the factors that ultimately shape the composition of the human microbiota? Is the composition of the human microbiota a cause or just a consequence of disease? Nevertheless, enormous progress has been made, and recent technical advances in the field of omics technologies combined with intelligent integration of the various layers of data will pave the way for further ground-breaking discoveries. The advent of a large collaborative project like BIOMAP will enable the integration of patient cohorts, data and knowledge in unprecedented proportions. Several challenges remain, however, including how to properly handle biological variability between individuals and over time, disease heterogeneity and various technical issues. The BIOMAP consortium constitutes a unique opportunity with a potential to bridge the gap between current problems and solutions, filling important gaps of knowledge.

## CONFLICT OF INTEREST

Authors have no conflict of interest.

## AUTHOR CONTRIBUTIONS

HA, HS and NF involved in conceptualization and project administration. NF, HS, PO, LM, MH, CB and JS involved in visualization. HA, HS, LM, ER, CB, HeA, MR, MH, PO, PB, CS, EB, AUN, CTH, BH, CF, KB, JS and SW involved in writing-original draft. HA, HS, LM, ER, CB, HeA, MR, MH, NF, PO, PB, CS, FK, KE, DG, EB, AUN, CTH, BH, CF, KB, JS and SW involved in writing-review and editing.

## DATA AVAILABILITY STATEMENT

Not relevant for the review article.

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